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Synthesis of phosphinines and phosphinanes using zirconium chemistry

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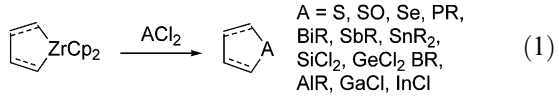
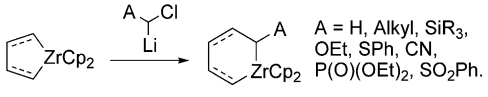
Abstract—Ring expansion of readily available zirconacyclopentadienes or zirconacyclopentanes by insertion of chloro(trimethylsilyl)methyllithium followed by metathesis with phosphorous trichloride provides a novel route to λ^3-phosphinines (phosphabenzenes) or phosphinanes.

Zirconacyclopentanes, Zirconacyclopentenes and Zirconacyclopentadienes are readily formed by the inter- or intramolecular co-cyclisation of alkenes and/or alkynes around a zirconocene ('Cp_2Zr') equivalent[1] and undergo metathesis with elements from groups III–VI of the periodic table to afford a variety of five-membered heterocycles (Eq. 1),[2] most relevantly phospholes[3] and phospholanes.[4] The use of zirconium chemistry to make phosphorous compounds including phosphacycles has recently been reviewed.[5] We have shown that five-membered zirconacycles may be readily ring expanded by insertion of a wide variety of carbenoids (R^1R^2CLiX) to afford six-membered zirconacycles (Eq. 2).[6] We now report the first example of further elaboration of some of these six-membered zirconacycles to provide a novel route to phosphacycles.



(1)



(2)

Our initial target was the synthesis of λ^3-phosphinines (phosphabenzenes), which have an interesting coordination chemistry,[3a,7] and are useful ligands in catalysis.[8]

Initially reported by Märkl[9] in 1966, other syntheses of λ^3-phosphinines have been developed,[10] of which some use zirconium chemistry for elaboration,[11] but they are still relatively inaccessible. Our proposed route to λ^3-phosphinines required the carbenoid ring expansion of a zirconacyclopentadiene, something we had previously only achieved when the carbon adjacent to the zirconium was unsubstituted.[12] An indication that we could overcome this limitation came from the observation that the carbenoid chloro(trimethylsilyl)methyllithium inserted into the substituted alkenyl–zirconium bonds of a zirconacyclopentene.[6a] Confirmation came both from our early observations, and Takahashi's publication of the ring expansion of a variety of zirconacyclopentadienes with chloro(trimethylsilyl)methyllithium to afford zirconacyclohexadienes.[13]

Zirconacycles **1a** and **1b** were formed by reaction of the Negishi reagent (Cp_2ZrBu_2) with 2 equiv of 4-octyne or 2-hexyne (2 h, room temperature), respectively (Scheme 1).[14] Addition to chloro(trimethylsilyl)methyllithium (1.2 equiv), generated by deprotonation of chloromethyltrimethyl-silane with *s*-BuLi/TMEDA, at −78 °C[15] and stirring for 1 h afforded the zirconacyclohexadienes **2**.[13] Reaction with PCl_3 at −78 °C and warming to room temperature gave the desired phosphinines **4a** and **4b** presumably via metathesis with loss of Cp_2ZrCl_2 to afford **3** followed by elimination of Me_3SiCl. Work-up by filtration through a pad of Celite under an argon atmosphere afforded material of ≈60% purity with NMR yields (against a standard) of 37% (**4a**) and 33% (**4b**). Unfortunately the λ^3-phosphinines were found to be very unstable to distillation and chromatography and could not be obtained analytically pure. Instead

Keywords: Phosphinine; Phosphinane; Phosphinic acid; Zirconacycle; Carbenoid.
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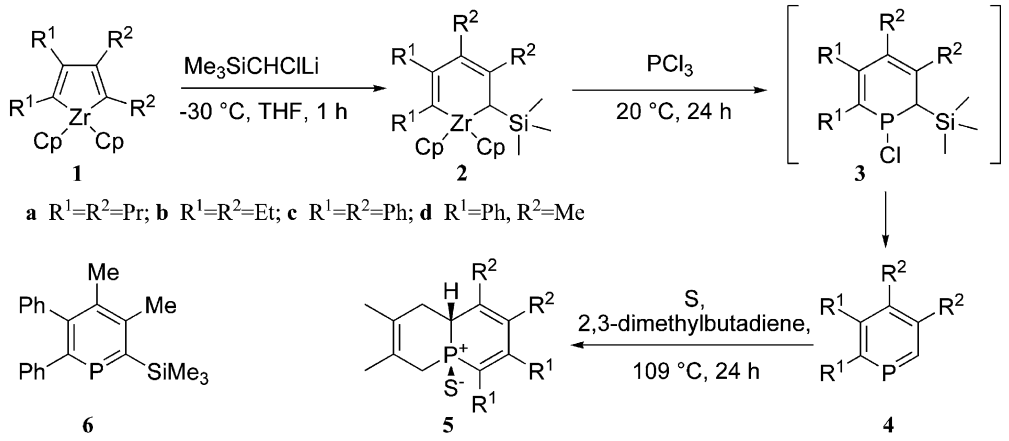


Scheme 1.

the crude phosphines were reacted with sulfur and 2,3-dimethylbutadiene to afford the Diels–Alder adducts **5** as outlined by Mathey.[16] Pure adducts **5a** and **5b** were isolated in 9% and 20% yield, respectively, over four steps from Cp_2ZrCl_2. It is possible to regenerate the λ^3-phosphinines from these adducts by heating with tributylphosphine.[16] Synthesis of **4c** was attempted but chloro(trimethylsilyl)methyllithium would not insert into **1c**, presumably due to the phenyl rings sterically impeding the reaction.

The unsymmetrical zirconacyclopentadiene **1d** was formed by sequential treatment of $Cp_2Zr(DMAP)_2$ (DMAP = 4-dimethylaminopyridine) with diphenylacetylene and 2-butyne according to Livinghouse.[17] Insertion of chloro(trimethylsilyl)methyllithium occurred exclusively into the side adjacent to a methyl group (see below) to afford **2d**. Addition of PCl_3 (room temperature, 16 h) gave a 1:1 mixture of the expected phosphinine **4d** and the trimethylsilyl-substituted phosphinine **6** derived by loss of HCl from **3d**, in a combined NMR yield of 34%. We initially attributed the formation of **6** to the presence of the DMAP base in the reaction mixture, however, neither increasing the concentration of DMAP, or adding excess diethylamine to the reaction mixture affected the ratio of **4d** to **6** formed. Also, addition of DMAP (2 equiv) to the reaction of zirconacycle **2a** with PCl_3 gave no 2-trimethylsilylphosphinine. Reaction of the mixture of **4d** and **6** with sulfur and 2,3-dimethylbutadiene gave the adduct **5d** as a yellow crystalline solid in 13% overall yield from Cp_2ZrCl_2. Interestingly, no Diels–Alder adduct was formed from **6**.[18] Crystals of **5d** were grown from methanol by slow evaporation and the structure obtained by X-ray crystallography (Fig. 1).[19] The X-ray structure confirmed the regiochemistry of the initial carbenoid insertion. It also shows the expected *cis* geometry of S1 and the hydrogen atom on C5.

For a further illustration of the use of carbenoid ring expansion of zirconacycles as a route to six-membered phosphacycles we looked at the synthesis of a phosphinane (phosphacyclohexane). Zirconacyclopentane **7** was prepared by co-cyclisation of 4,4-bis(methoxymethyl)hepta-1,6-diene using Cp_2ZrBu_2.[1] Ring expansion with chloro(trimethylsilyl)methyllithium afforded **8** in excellent yield.[6a] Reaction with PCl_3 was initially fast to form **9**, however, complete intramolecular metathesis to give **10** took 6 days at room temperature (Scheme 2). Unlike **3**, Me_3SiCl elimination from **10** was not observed. In view of the biological interest in phosphinic acids,[20] and to avoid problems of air sensitivity we oxidised **10** in situ with hydrogen peroxide to afford **11** as a 1:1 mixture of diastereoisomers in 36% overall yield. Surprisingly **11** was not protodesilylated by tetrabutylammonium fluoride, concentrated HCl or HF in pyridine.

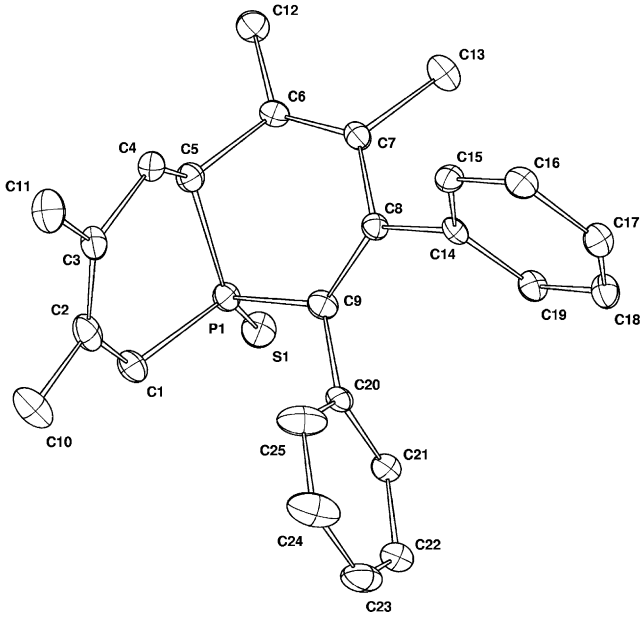
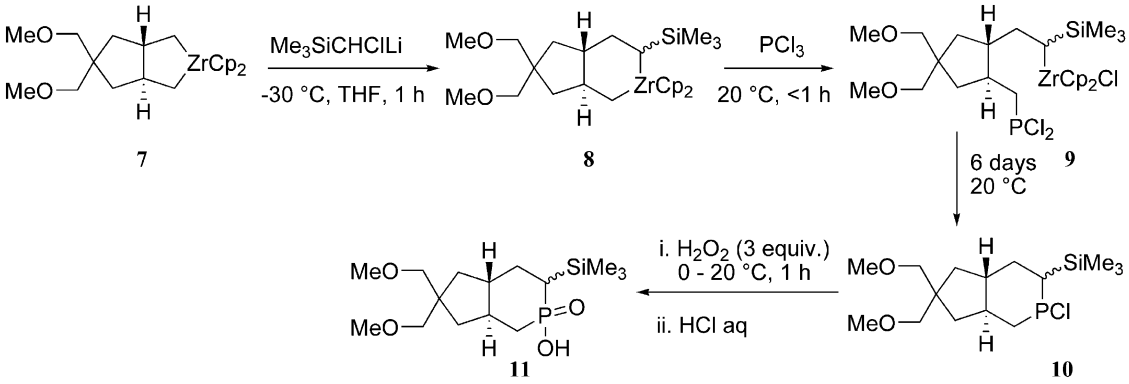


Figure 1. Crystal structure of **5d**. Thermal ellipsoids drawn at the 30% probability level.

In conclusion we have shown that carbenoid ring expansion of five- to six-membered zirconacycles followed by metathesis with PCl_3 is a viable, if currently low yielding, route to six-membered phosphacycles including λ^3-phosphinines.[21] The method should be applicable to



Scheme 2.

the synthesis of a wide variety of other six-membered heterocycles, particularly benzenoid heteroaromatics, of the elements indicated in Eq. 1.

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18. Desilylation at some point in the reaction sequence thus giving **5d** cannot be ruled out.
19. Crystallographic data (excluding structure factors) for **5d** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 243514. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk).

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21. 2,3-Dimethyl-5,6,7,8-tetraethyl-1,8a-dihydro-4*H*-4a-phospha-naphthalene 4a-sulfide **5b**. Cp_2ZrCl_2 (292 mg, 1 mmol) in THF (5 mL) was cooled to −78 °C before *n*-BuLi (0.8 mL of a 2.5 M soln. in hexanes, 2 mmol) was added dropwise. After 0.5 h, 3-hexyne (173 mg, 2.1 mmol) in THF (5 mL) was added and the reaction mixture was warmed to room temperature and stirred for 2 h. To Me_3SiCH_2Cl (147 mg, 1.2 mmol) and TMEDA (140 mg, 1.2 mmol) in THF (5 mL) at −78 °C was added dropwise *s*-BuLi (0.92 mL of 1.3 M soln. in cyclohexane, 1.2 mmol) and the mixture stirred for 1 h. The red zirconacycle solution was cooled to −78 °C then added via cannular to the carbenoid solution. After 1 h at −78 °C, PCl_3 (0.25 mL, 2.5 mmol) was added and after 1 h the mixture was warmed to room temperature and stirred for 16 h. All volatiles were removed in vacuo and the residue extracted into hexane (8 × 50 mL). The hexane extracts were filtered through Celite under a flow of argon then solvent removed to afford crude 2,3,4,5-tetraethylphosphinine **4b** as a yellow oil (113 mg, 60% pure by mass, 33%). NMR ($CDCl_3$) δ/ppm: ^{31}P (121 MHz) 190.95; ^{1}H (300 MHz) 8.37 (1H, d, J_{PH} = 36.0 Hz, C*H*), 3.03 (2H, dt, J_{PH} = 25.5 Hz, J_{HH} = 7.4 Hz, CH_2), 2.90–2.69 (6H, m, 3 × CH_2), 1.37 (3H, t, J_{HH} = 7.4 Hz, CH_3), 1.30 (3H, t, J_{HH} = 7.4 Hz, CH_3), 1.23 (3H, t, J_{HH} = 7.4 Hz, CH_3), 1.12 (3H, t, J_{HH} = 7.4 Hz, CH_3); ^{13}C (75 MHz) 170.19 (d, J_{PC} = 46.0 Hz, *C*H), 151.89 (d, J_{PC} = 43.7 Hz, *C*), 147.16 (d, J_{PC} = 6.9 Hz, *C*), 146.97 (d, J_{PC} = 4.8 Hz, *C*), 143.01 (d, J_{PC} = 18.0 Hz, *C*), 29.59 (d, J_{PC} = 35.6 Hz, *C*H$_2$), 29.28 (d, J_{PC} = 3.4 Hz, *C*H$_2$), 23.34 (d, J_{PC} = 1.7 Hz, *C*H$_2$), 23.02 (d, J_{PC} = 1.1 Hz, *C*H$_2$), 18.59 (d, J_{PC} = 12.4 Hz, *C*H$_3$), 15.87 (*C*H$_3$), 15.61 (d, J_{PC} = 1.7 Hz, *C*H$_3$), 15.36 (d, J_{PC} = 4.0 Hz, *C*H$_3$). LRMS (EI): *m*/*z* 208 (M,100%), 193 (M−Me, 54), 179 (M−Et, 89), 151 (23), 133 (29), 105 (M, 21), 91 (M, 37). HRMS (EI): $C_{13}H_{21}P$ requires *m*/*z* 208.1381, found 208.1380.In a sealed tube **4b** (113 mg, 60% purity, 0.33 mmol), sulfur (17 mg, 0.53 mmol), 2,3-dimethylbutadiene (0.40 mL, 3.5 mmol) in toluene (2 mL) were heated for 24 h at 109 °C. Purification by column chromatography (SiO_2, 20% ether in petrol) gave the title compound **5b** as a pale yellow oil, 65 mg, 20% over four steps. NMR ($CDCl_3$) δ/ppm ^{31}P (121 MHz) 22.55; ^{1}H (300 MHz) 3.40–1.78 (13H, m), 1.68 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.13 (3H, t, J = 7.7 Hz, CH_3), 1.08 (3H, t, J = 7.7 Hz, CH_3), 0.98 (3H, t, J = 7.4 Hz, CH_3), 0.95 (3H, t, J = 7.7 Hz, CH_3); ^{13}C (75 MHz) 149.52 (d, J_{PC} = 4.0 Hz, *C*), 136.22 (d, J_{PC} = 10.2 Hz, *C*), 133.32 (d, J_{PC} = 18.1 Hz, *C*), 128.38 (d, J_{PC} = 9.0 Hz, *C*), 124.91 (d, J_{PC} = 76.9 Hz, *C*), 121.12 (d, J_{PC} = 6.2 Hz, *C*), 37.07 (d, J_{PC} = 54.8 Hz, *C*H), 36.76 (d, J_{PC} = 4.5 Hz, *C*H$_2$), 34.55 (d, J_{PC} = 50.3 Hz, *C*H$_2$), 27.18 (d, J_{PC} = 5.7 Hz, *C*H$_2$), 21.80 (d, J_{PC} = 11.3 Hz, *C*H$_2$), 21.23 (d, J_{PC} = 1.7 Hz, *C*H$_2$), 20.67 (d, J_{PC} = 10.7 Hz, *C*H$_2$), 20.56 (d, J_{PC} = 11.3 Hz, *C*H$_3$), 19.42 (d, J_{PC} = 1.1 Hz, *C*H$_3$), 14.24 (d, J_{PC} = 4.0 Hz, *C*H$_3$), 13.96 (d, J_{PC} = 2.8 Hz, *C*H$_3$), 13.66 (d, J_{PC} = 2.8 Hz, *C*H$_3$), 11.65 (d, J_{PC} = 2.1 Hz, *C*H$_3$). LRMS (EI): *m*/*z* 322 (M^+, 100%), 307 (M^+−Me, 12%), 289 (M^+−Et, 33%), 275 (37%), 240 (29%), 208 (21%), 177 (91%), 161 (23%), 147 (32%), 133 (33%), 91 (34%). HRMS (EI): $C_{19}H_{31}PS$ requires *m*/*z* 322.1884, found 322.1893.